



Role of *Streptococcus pneumoniae* in the era of pandemic influenza

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Pneumonia is the leading infectious cause of death, yet little research is devoted to its treatment and prevention. Influenza may progress to bacterial pneumonia, but the extent of the contribution of bacteria to influenza associated pneumonia morbidity and mortality is unknown. Pneumococcal conjugate vaccine (PCV) has been used as a probe to determine the role of the pneumococcus in super – infection of seasonal influenza associated pneumonia. In a double blind randomized trial of 9 – valent PCV it was shown that PCV prevented clinical pneumonia associated influenza by 45%[1]. More recently it has been shown that States in the USA that quickly adopted 7 valent pneumococcal conjugate vaccination in infants had less hospitalization of infants in those States immediately after PCV7 introduction, than in States that were slower to introduce PCV7[2]. This suggests that a major fraction of influenza associated pneumonias in children may be due to pneumococcal super-infection.

An analysis of the contemporary literature of the 1918 influenza pandemic suggests that, in contrast to prevailing wisdom today, >80% of deaths occurred ≥ 7 days after onset of symptoms (influenza resolved in < 6 days in > 90% of patients). In fact, the time to mortality of untreated pneumococcal pneumonia follows an identical time course to the 1918 influenza deaths[3]. A recent audit of autopsy specimens from the 1918 epidemic found bacterial infection in all of 58 specimens of lung tissue that were found from influenza deaths during the pandemic[4]. In studies of blood cultures taken from living patients with pandemic influenza associated pneumonia in 1918, bacteria were isolated from blood in 16% of the patients who had pneumonia following influenza, compared to <1% bacteremia among the uncomplicated

influenza patients[5]. Furthermore, in patients from whom specimens could be cultured from pleural fluid or lung tissue, bacteria were found during life in 80%[5]. Among the bacterial species identified, the pneumococcus was predominant, being isolated in up to 50% of patients, with hemolytic streptococci the second most common pathogen, and staphylococci relatively rarely isolated[5]. A number of bacterial vaccine studies were performed during the 1918 pandemic. These studies were poorly designed by today's standard of randomized double blind trials, but a re – analysis of these studies, using influenza cases as the denominator and using pneumonia and death as outcomes, suggest that pneumococcal killed bacterial vaccines may have prevented both pneumonia and deaths[6].

Recent autopsy data from the current H1N1 pandemic in the USA[7] found bacteria in 29% of 77 confirmed deaths caused by the 2009 H1N1 influenza A pandemic. The predominant pathogen was again the pneumococcus followed by group A streptococci and staphylococci. As the US population of infants was highly immunized with PCV7 at this time with clear evidence of herd immunity protecting adults from non – bacteremic pneumococcal pneumonia[2], it is not surprising that the pneumococcal serotypes identified were largely less virulent non – PCV7 vaccine types. A similar study of autopsies of 2009 H1N1 victims in New York found 55% to have bacterial co – infection[8]. Finally a smaller autopsy study from Brazil among 21 patients found 38% with bacterial infection detected by PCR with the pneumococcus the predominant pathogen[9]. Among 337 patients mechanically ventilated with H1N1 infection in Argentina, 25% had a bacterial infection identified, with the pneumococcus the predominant bacterial pathogen identified and co – infection with the pneumococcus was an independent predictor of death[10]. Similar data have recently been reported from the UK with 40% of fatal pediatric cases presumed or confirmed to have bacterial co –infection[11]. Finally, a case control study from Brazil has found that among patients 6 to 55 years of age, controlling for co-morbidity and for infection with RSV, detection of the pneumococcus in the nasopharynx was associated with a greatly increased risk of hospitalization or death due to H1N1. These studies suggest that a large fraction of hospitalizations and deaths in otherwise healthy individuals during 2009 may have been due to bacterial co – infection, and pneumococcal infection in particular.

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